Respiratory Medicine (2015) xx, 1–10

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A randomised, double-blind, four-way, crossover trial comparing the 24-h FEV_1 profile for once-daily versus twice-daily treatment with olodaterol, a novel long-acting β_2-agonist, in patients with chronic obstructive pulmonary disease

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Received 1 December 2014; accepted 6 February 2015

KEYWORDS
Olodaterol;
Long-acting beta-2-agonist;
COPD

Summary
Background: This randomised, double-blind, four-way, crossover, Phase II study compared the 24-h forced expiratory volume in 1 s (FEV_1) profile of alternative dosing frequencies of two total daily doses of olodaterol (5 and 10 μg) in patients with chronic obstructive pulmonary disease (COPD).
Methods: Patients received olodaterol 2 μg twice daily (BID), 5 μg BID, 5 μg once daily (QD) and 10 μg QD in a randomised sequence over 3-week treatment periods. Co-primary end points

Abbreviations: AE, adverse event; AUC_{0-12}, area under the curve from 0 to 12 h; AUC_{0-24}, area under the curve from 0 to 24 h; AUC_{12-24}, area under the curve from 12 to 24 h; BID, twice daily; CI, confidence interval; COPD, chronic obstructive pulmonary disease; $C_{pre,ss}$, plasma concentration prior to dosing; $C_{0.167,ss}$, plasma concentration at 10 min post-dosing; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LABA, long-acting β_2-agonist; QD, once daily.

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http://dx.doi.org/10.1016/j.rmed.2015.02.005

were FEV_1 area under the curve from 0 to 12 h (AUC_{0-12}) and area under the curve from 12 to 24 h (AUC_{12-24}) responses. Additional lung-function responses, pharmacokinetics and safety were assessed.
Results: 47 patients were treated. All olodaterol doses provided significant increases in FEV_1 versus baseline ($p < 0.001$) and FEV_1 time profiles were nearly identical for olodaterol 5 and 10 μg QD. Olodaterol 5 μg QD demonstrated improved FEV_1 AUC_{0-12} and similar AUC_{12-24} versus 2 μg BID. Olodaterol 5 μg QD showed slightly increased FEV_1 AUC_{0-12} but lower AUC_{12-24} compared to 5 μg BID. Bronchodilation over 24 h was similar for olodaterol 5 μg QD and BID. All doses were well tolerated.
Conclusions: Olodaterol 5 μg QD is efficacious in COPD, with a superior bronchodilatory profile compared to 2 μg BID, which is close to the same total daily dose, and a similar degree of bronchodilation over 24 h compared with double the daily dose (administered as 10 μg QD or 5 μg BID).
Trial registration: ClinicalTrials.gov: NCT00846768.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by non-reversible airflow limitation and a progressive deterioration in lung function [1—4]. β_2-adrenoceptor agonists are among the most potent rapidly acting bronchodilators, providing therapeutic benefits in the treatment of COPD [5]. The first generation of long-acting β_2-agonists (LABAs), which include salmeterol and formoterol, have a 12-h duration of action and consequently require twice-daily (BID) dosing to ensure effective bronchodilation over 24 h [5]. More recently, LABAs with a longer duration of action have been developed [6] allowing for once-daily (QD) dosing, which may improve treatment adherence in patients with COPD [7].

Olodaterol is a novel, enantiomerically pure, selective LABA [8]. The preclinical profile of olodaterol shows that it has high selectivity for the human β_2-adrenoceptor, with a potent, near full-agonist response *in vitro*, and provides effective bronchoprotection over 24 h in anaesthetised guinea pigs and dogs *in vivo* [9]. Together, these data suggested that 24-h bronchodilation may be achieved with QD administration in humans.

Single-dose administration of olodaterol has been shown to provide effective bronchodilation over 24 h in patients with COPD [4] and effective bronchoprotection against inhaled methacholine for up to 32 h in patients with asthma [10].

The study presented here is one of two trials designed to determine the optimum dose and frequency of olodaterol in patients with COPD. In a 4-week Phase II study (NCT00452400) evaluating the bronchodilatory efficacy of four QD doses of olodaterol (2, 5, 10 and 20 μg), olodaterol 10 and 20 μg QD were shown to be on the plateau of the dose—response curve, while olodaterol 2 μg QD was on the steep part of the curve [11]. This report describes the other Phase II study, which was designed to further evaluate the bronchodilatory activity of olodaterol by comparing the 24-h forced expiratory volume in 1 s (FEV_1) profiles of QD olodaterol (5 μg and 10 μg) and BID olodaterol (2 μg and 5 μg) dosing regimens following 3 weeks of treatment in patients with COPD. The 5 μg and 10 μg QD doses were selected for further evaluation in long-term Phase III studies, which have now demonstrated 24-h efficacy and satisfactory tolerability in patients with moderate to very severe COPD [12—15].

Methods

Patients

Patients were enrolled into the study if they met the following inclusion criteria: age $\geq$ 40 years; current or ex-smokers with a smoking history of $>$ 10 pack-years; post-bronchodilator $FEV_1 < 80\%$ of predicted normal; and post-bronchodilator FEV_1/forced vital capacity (FVC) $< 70\%$. Key exclusion criteria were: a significant disease other than COPD (defined by the investigator as a disease that may put the patient at risk by participating in the study, influence study outcomes or cause concern with regards to the patient's ability to participate in the study); history of asthma; history of myocardial infarction within 1 year of the screening visit; unstable or life-threatening cardiac arrhythmia or hospitalisation for heart failure within the past year; or experience of any respiratory infection or COPD exacerbation 6 weeks prior to initiation of the study or during the baseline period.

Study design

This was a Phase II, randomised, double-blind, four-way, crossover study (registered with ClinicalTrials.gov: NCT00846768). Patients completed a pre-treatment baseline 24-h FEV_1 profile and then were randomly assigned into four groups to receive each of the following treatments in a randomised sequence: olodaterol 2 μg BID, 5 μg BID, 5 μg QD and 10 μg QD. Each administration of olodaterol comprised two actuations of the Respimat® inhaler. Each treatment period lasted for 3 weeks, with no washout in between. Patients were evaluated for 14 days following completion of the study (Fig. 1).

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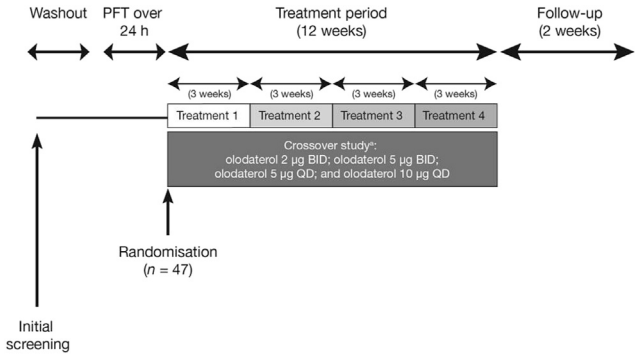

Figure 1 Study design.

Patients were permitted to use inhaled corticosteroids and short-acting anticholinergics throughout the study, as needed, and salbutamol (100 µg) was administered as rescue medication, if required.

The study was approved by local ethics committees and carried out according to the Declaration of Helsinki and local regulations. Prior to study initiation, the protocol was approved by the local Institutional Review Board, Independent Ethics Committee and the Competent Authority. All patients provided written, informed consent prior to the study commencing.

Assessments

FEV_1 was the primary criterion for evaluation in this study. All qualifying pulmonary function tests (FEV_1 and FVC) were conducted during the screening visit. One week following the initial screening visit, and appropriate washout for bronchodilators, all patients underwent pulmonary function testing over 24 h to determine the pre-treatment baseline 24-h FEV_1 time profile. FEV_1 and FVC pulmonary function tests were performed at the end of each 3-week treatment period (Visits 2—6). Pulmonary function tests were always started at approximately the same time of day for each patient. All spirometry was performed according to American Thoracic Society/European Respiratory Society criteria [16]. Daily trial medication and daily rescue medication use (salbutamol 100 µg per actuation) were recorded in paper diaries for assessment of adherence.

Safety measurements included laboratory tests, vital signs (blood pressure and pulse rate) and 12-lead electrocardiogram. All adverse events (AEs), irrespective of causality, were recorded at each visit.

Plasma concentrations of olodaterol were assessed by taking 9—10 mL of blood from a forearm vein prior to and 10 min after drug inhalation at the end of each 3-week treatment period. Urine samples were collected from 0 to 12 and 12 to 24 h after dosing for the QD treatments, and from 0 to 12 h after the morning and evening dose for the BID doses at the end of each 3-week treatment period. Plasma and urine concentrations were determined by validated methods using high-performance liquid chromatography, coupled to tandem mass spectrometry.

Study outcomes

The co-primary efficacy end points assessed were FEV_1 area under the curve from 0 to 12 h (AUC_{0-12}) and FEV_1 area under the curve from 12 to 24 h (AUC_{12-24}) responses from baseline after 3 weeks of treatment. Secondary efficacy variables included FEV_1 area under the curve from 0 to 24 h (AUC_{0-24}), peak and trough FEV_1 response following 3 weeks of treatment, corresponding FVC parameters, and FEV_1 and FVC measurements at individual time points over a 24-h period (from which the FEV_1 and FVC 24-h time profiles could be constructed). Safety end points, including AEs and vital signs, were assessed in all patients who received at least one dose of the study drug. Pharmacokinetic parameters evaluated following 3 weeks of treatment included the olodaterol plasma concentration prior to dosing ($C_{pre,ss}$ or 'trough') and at 10 min post-dosing ($C_{0.167,ss}$), and the fraction of olodaterol dose eliminated in urine within the dosing interval.

Statistical analysis

A sample size of 48 randomised patients provided $\geq$ 90% power to detect a difference between olodaterol and baseline of 90 mL in FEV_1 AUC_{0-12} and of 80 mL in FEV_1 AUC_{12-24}, based on an estimated standard deviation of 0.16 L for FEV_1 AUC_{0-12} and 0.14 L for FEV_1 AUC_{12-24} and a conservative estimated randomised discontinuation rate of 25%.

The primary and secondary efficacy end points were based on the full analysis set, which included all patients with baseline data and evaluable post-dosing data for at least the co-primary end points. Both primary and secondary end points were analysed using a mixed-effects repeated measures model with 'treatment' and 'period' as fixed effects and 'period' as a repeated effect, with 'patient' as the repeated subject and a compound symmetry covariance structure. The model did not contain treatment sequence, as, owing to the trial design and half-life of the study drug, there was no expectation that carry over would occur.

Safety and pharmacokinetic analyses

All safety analyses were performed on the treated set, which included all patients who received at least one dose of the study drug. Analyses of AEs, laboratory data, vital signs and pharmacokinetic parameters were descriptive in nature. Pharmacokinetic parameters were determined by non-compartmental analysis of the plasma/urine concentration-time data using the WinNonlin™ software (Professional, Version 5.2, Pharsight Corporation, Mountain View, California, USA).

Results

Patient population

The trial was conducted from 16 February 2009 to 20 July 2009. A total of 56 patients at five centres in Belgium and the Netherlands were enrolled into the study, 47 of whom

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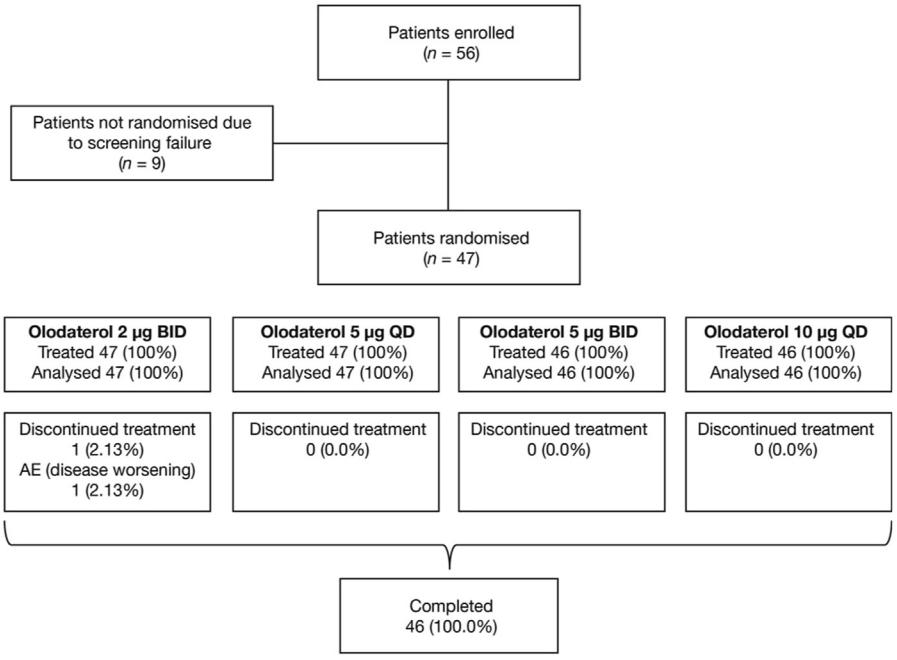

Figure 2 CONSORT diagram illustrating participant flow.

were randomised to receive study medication; one patient was discontinued prematurely due to worsening of disease (Fig. 2). There were a greater number of men than women participating in the study, and patients had a mean age of 65.6 years, with a mean smoking history of 39.5 pack-years (Table 1).

Efficacy

Lung function

All dosing regimens provided significant increases in the co-primary end points of FEV_1 AUC_{0-12} and AUC_{12-24} after 3 weeks of treatment compared to baseline ($p < 0.001$) (Table 2). The magnitude of response ranged from 0.155 L (olodaterol 2 µg BID) to 0.209 L (olodaterol 5 µg QD) for FEV_1 AUC_{0-12}, and 0.149 L (olodaterol 10 µg QD) to 0.201 L (olodaterol 5 µg BID) for FEV_1 AUC_{12-24}. All dose regimens also demonstrated significant increases in the secondary end point of FEV_1 AUC_{0-24} compared with baseline ($p < 0.001$) (Table 2), ranging from 0.160 L (olodaterol 2 µg BID) to 0.195 L (olodaterol 5 µg BID).

In addition, all dose regimens demonstrated increases in FEV_1 at all individual time points over the 24-h observation period (Fig. 3a).

For comparisons across dosing regimens, the primary focus was to compare olodaterol 5 µg QD with other QD and BID regimens, since olodaterol 5 µg QD was the lowest QD dose taken forward into the Phase III clinical programme.

Table 1 Baseline patient demographics (treated set).

Patients, n (%)	47 (100.0)
Sex, n (%)	
Male	36 (76.6)
Female	11 (23.4)
Mean (SD) age, years	65.6 (8.0)
Mean (SD) body mass index, kg/m^2	26.2 (4.0)
Smoking status, n (%)	
Ex-smoker	30 (63.8)
Current smoker	17 (36.2)
Mean (SD) smoking history, pack-years	39.5 (19.7)
Pre-bronchodilator, L	
Mean (SD) FEV_1	1.26 (0.32)
Mean (SD) % of predicted normal FEV_1	45.1 (10.1)
Post-bronchodilator, L	
Mean (SD) FEV_1	1.44 (0.38)
Mean (SD) % of predicted normal FEV_1	51.7 (12.0)
Mean (SD) change from pre-bronchodilator FEV_1	0.18 (0.15)
Mean (SD) post-bronchodilator FEV_1/FVC, %	45.9 (8.8)

SD, standard deviation.

2 µg BID versus 5 µg QD

The FEV_1 AUC_{0-12} response for olodaterol 5 µg QD was 0.209 L compared with 0.155 L for olodaterol 2 µg BID, while the FEV_1 AUC_{12-24} response was 0.155 L (olodaterol 5 µg QD) and 0.167 L (olodaterol 2 µg BID). Over the complete 24-h observation period, the FEV_1 AUC_{0-24} response was 0.182 L for olodaterol 5 µg QD compared with 0.160 L for olodaterol 2 µg BID (difference = 0.022 L, 95% confidence interval [CI]: −0.005, 0.049) (Table 3; Fig. 3b).

5 µg QD versus 10 µg QD

Near identical FEV_1 AUC_{0-12} responses of 0.209 L and 0.204 L were reported following treatment with olodaterol 5 µg QD and 10 µg QD. The FEV_1 AUC_{12-24} response for olodaterol 5 QD was 0.155 L compared with 0.149 L for olodaterol 10 QD, while the FEV_1 AUC_{0-24} responses were 0.182 L (olodaterol 5 µg QD) compared with 0.176 L (olodaterol 10 µg QD) (difference = −0.006 L, 95% CI: −0.033, 0.021) (Table 3; Fig. 3c).

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Table 2 Adjusted mean FEV_1 AUC_{0-12} response, FEV_1 AUC_{12-24} response and FEV_1 AUC_{0-24} response after 3 weeks of treatment.

Doses	Adjusted mean difference (standard error)		
	FEV_1 AUC_{0-12}, L	FEV_1 AUC_{12-24}, L	FEV_1 AUC_{0-24}, L
Baseline	1.187 (0.052)	1.132 (0.048)	1.160 (0.050)
Olodaterol 2 μg BID	0.155 (0.024)	0.167 (0.022)	0.160 (0.022)
Olodaterol 5 μg BID	0.189 (0.024)	0.201 (0.022)	0.195 (0.022)
Olodaterol 5 μg QD	0.209 (0.024)	0.155 (0.022)	0.182 (0.022)
Olodaterol 10 μg QD	0.204 (0.024)	0.149 (0.022)	0.176 (0.022)

Patients: 5 μg QD, $n = 47$; 2 μg BID, $n = 46$ ($n = 45$; AUC_{0-12} and AUC_{0-24}); 10 μg QD, $n = 46$; 5 μg BID, $n = 46$, $p < 0.001$ for all doses versus baseline.

5 μg QD versus 5 μg BID

FEV_1 AUC_{0-12} responses of 0.209 L and 0.189 L were reported following treatment with 5 μg QD and 5 μg BID, respectively. The FEV_1 AUC_{12-24} response for olodaterol 5 μg QD was 0.155 L compared with 0.201 L for olodaterol 5 μg BID. The FEV_1 AUC_{0-24} response was 0.182 L for olodaterol 5 μg QD compared with 0.195 L for olodaterol 5 μg BID (difference = −0.013 L, 95% CI: −0.040, 0.014) (Table 3; Fig. 3d).

As this was the first study to include BID doses of olodaterol, another comparison of interest was olodaterol 5 μg BID compared with olodaterol 2 μg BID. There was a consistent increase in the FEV_1 response for olodaterol 5 μg BID compared with olodaterol 2 μg BID over the full 24-h observation period (Fig. 3e), with similar differences observed in the FEV_1 AUC_{0-12}, FEV_1 AUC_{12-24} and FEV_1 AUC_{0-24} responses (0.033, 0.035 and 0.035 L, respectively) (Table 3).

The comparisons across dosing regimens for FEV_1 peak response from 0 to 3 h were consistent with the results for the FEV_1 AUC_{0-12} response, while comparisons across dosing regimens for trough FEV_1 response were consistent with the results for FEV_1 AUC_{12-24} response (Table 4). Results for FVC responses were generally consistent with FEV_1 responses (Fig. 4).

Pharmacokinetics

Trough plasma concentrations ($C_{pre,ss}$) of olodaterol 2 μg BID and 5 μg QD were mostly below the limit of quantification (2.0 pg/mL); therefore, the geometric mean for these doses was not calculated. Trough plasma concentrations were measurable in more than one-third of patients following inhalation of olodaterol 5 μg BID and 10 μg QD. Data showed that geometric mean values were comparable between both treatments (2.92 and 2.97 pg/mL, respectively). The $C_{0.167,ss}$ olodaterol concentrations following inhalation of 2 μg BID were mostly below the limit of quantification; the geometric mean $C_{0.167,ss}$ values for olodaterol 5 μg QD, 5 μg BID and 10 μg QD were 3.52, 4.28 and 5.78 pg/mL, respectively (Table 5). The fraction of dose excreted via urine within the dosing interval was similar across all dose groups (3.27−3.61%). The amount of olodaterol excreted via urine within 24 h was similar between 5 μg BID (340 ng) and 10 μg QD (343 ng), while there was a slight difference in the daily amount of olodaterol excreted in urine between 2 μg BID (136 ng) and 5 μg QD (181 ng) due to the difference in total daily dose (Table 5).

Safety

Overall, 62% of patients experienced at least one AE (Table 6), the majority of which were mild to moderate in nature (only one patient receiving olodaterol 2 μg BID experienced a serious AE of COPD exacerbation and pneumonia, which was not considered to be related to the study drug). The most frequently reported AE was nasopharyngitis, which was reported by three patients (6.5%) receiving 10 μg QD, three patients (6.5%) receiving 5 μg BID and one patient (2.1%) receiving each of the 5 μg total daily doses of olodaterol (Table 6). Drug-related AEs were reported by seven patients (Table 7). Monitoring of other safety parameters, including 12-lead electrocardiogram, blood pressure, pulse rate and standard laboratory testing, did not reveal any clinically relevant changes from baseline.

Discussion

The results from this randomised, double-blind, four-way, crossover study add to a growing body of evidence that QD administration with olodaterol delivered by the Respimat® inhaler provides effective bronchodilation over a complete 24-h period in patients with COPD [4]. The study has also provided new insights into the dose-response and dose-frequency profile of olodaterol by comparing the 24-h bronchodilatory profile of olodaterol when administered as a QD (olodaterol 5 and 10 μg) or BID (olodaterol 2 and 5 μg) dosing regimen.

A comparison of the FEV_1 time profiles for olodaterol 5 μg QD and olodaterol 2 μg BID (Fig. 3b) shows a separation between the two dose regimens in the 0 to 12 h interval similar to the separation observed for olodaterol 5 μg QD and olodaterol 2 μg QD in the early daily dose-response studies. The additional peak as a result of the second evening dose of olodaterol 2 μg BID resulted in a similar degree of bronchodilation for olodaterol 5 μg QD and olodaterol 2 μg BID in the 12 to 24 h interval. Thus, overall, olodaterol 5 μg QD provided a superior bronchodilating profile over 24 h compared with olodaterol 2 μg BID. One potential limitation of the current study was the unavailability of olodaterol 2.5 μg BID, as this dose of olodaterol was not available in the Respimat® device when the study was initiated. Ideally, an olodaterol 2.5 μg dose would have been included in this study to allow for direct comparison between olodaterol 2.5 μg BID and 5 μg QD (i.e. the same total daily dose). However, data calculated for a theoretical 2.5 μg BID dose by interpolating between FEV_1 values

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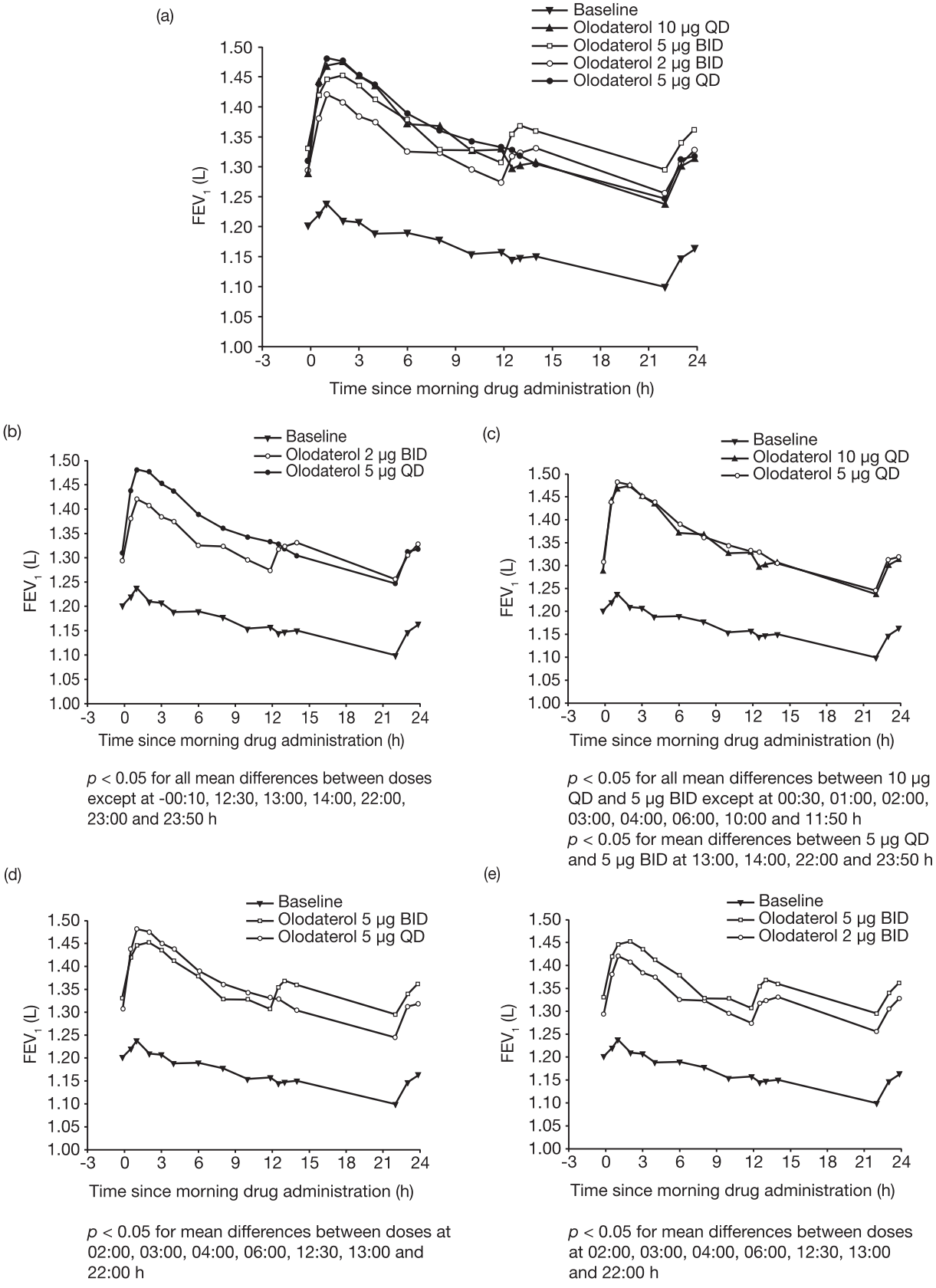

Figure 3 Adjusted mean FEV_1 AUC_{0-24} for olodaterol versus baseline after 3 weeks of treatment for: (a) all doses; (b) 5 µg QD and 2 µg BID; (c) 5 and 10 µg QD; (d) 5 µg QD and 5 µg BID; and (e) 2 and 5 µg BID.

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Table 3 Adjusted mean difference between dose regimens in FEV_1 AUC_{0-12}, AUC_{12-24} and AUC_{0-24} after 3 weeks of treatment.

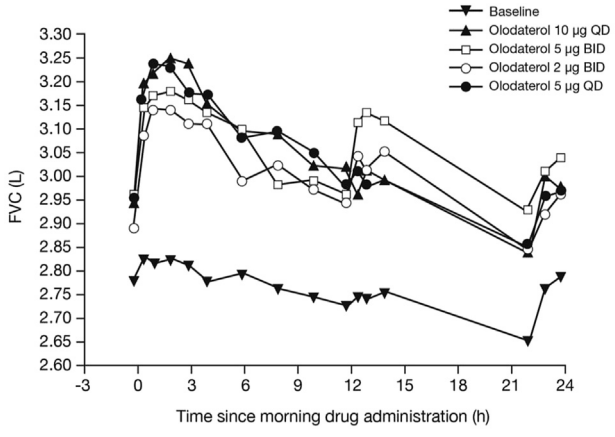
Doses	Adjusted mean difference (standard error) [95% CI]		
	FEV_1 AUC_{0-12}, L	FEV_1 AUC_{12-24}, L	FEV_1 AUC_{0-24}, L
5 μg QD vs 2 μg BID	0.054 (0.015) [0.025, 0.083]	−0.012 (0.015) [−0.041, 0.017]	0.022 (0.014) [−0.005, 0.049]
10 μg QD vs 5 μg QD	−0.006 (0.015) [−0.034, 0.023]	−0.006 (0.015) [−0.035, 0.024]	−0.006 (0.014) [−0.033, 0.021]
5 μg QD vs 5 μg BID	0.021 (0.015) [−0.008, 0.050]	−0.047 (0.015) [−0.076, −0.017]	−0.013 (0.014) [−0.040, 0.014]
5 μg BID vs 2 μg BID	0.033 (0.015) [0.004, 0.063]	0.035 (0.015) [0.005, 0.064]	0.035 (0.014) [0.007, 0.062]

Patients: 5 μg QD, $n = 47$; 2 μg BID, $n = 46$ ($n = 45$; AUC_{0-12} and AUC_{0-24}); 10 μg QD, $n = 46$; 5 μg BID, $n = 46$.

Table 4 Adjusted mean peak FEV_1 response from 0 to 3 h and FEV_1 trough response following 3 weeks of treatment.

Adjusted mean difference (standard error)			
Doses	Pre-dose FEV_1, L[a]	Peak FEV_1 from 0 to 3 h, L	FEV_1 at end of dosing interval, L[b]
Baseline	1.202 (0.051)	1.276 (0.054)	1.165 (0.052)
2 μg BID	0.093 (0.028)	0.187 (0.029)	0.163 (0.062)
5 μg BID	0.129 (0.028)	0.230 (0.029)	0.197 (0.062)
5 μg QD	0.108 (0.028)	0.249 (0.029)	0.153 (0.062)
10 μg QD	0.087 (0.028)	0.242 (0.029)	0.150 (0.062)

Patients: 5 μg QD, $n = 47$; 2 μg BID, $n = 45$ ($n = 46$; end of dosing interval); 10 μg QD, $n = 46$; 5 μg BID, $n = 46$, $p < 0.001$ (peak FEV_1, FEV_1 at end of dosing interval) and $p < 0.01$ (trough FEV_1) for all doses versus baseline.
[a] 10 min prior to dosing after 3 weeks.
[b] 23 h and 50 min post-dose after 3 weeks.



$p < 0.05$ for mean differences between 5 μg QD and 5 μg BID at 01:00, 08:00, 12:30, 13:00, 14:00 and 22:00 h
$p > 0.05$ for all mean differences between 10 μg QD and 5 μg QD
$p < 0.05$ for mean differences between 5 μg BID and 10 μg QD at 03:00, 08:00, 12:30, 13:00, 14:00 and 22:00 h
$p < 0.05$ for mean differences between 5 μg QD and 2 μg BID at 00:30, 01:00, 02:00 and 06:00 h
$p < 0.05$ for mean differences between 5 μg BID and 2 μg BID at 06:00, 13:00, 22:00 and 23:00 h

Figure 4 Adjusted mean FVC AUC_{0-24} for olodaterol QD (5 or 10 μg) or BID (2 or 5 μg) versus baseline after 3 weeks of treatment.

for olodaterol 2 μg BID and 5 μg BID (assuming a linear dose response between both) support the conclusions from the observed data, thus indicating that olodaterol 2 μg was a satisfactory dosing alternative to 2.5 μg in this study (Fig. 5).

Other key comparisons of interest in this study were between olodaterol 5 μg QD and dose regimens with double the daily dose, either according to a QD (olodaterol 10 μg) or BID (olodaterol 5 μg) regimen.

The 24-h bronchodilatory profile for olodaterol 5 μg QD and 10 μg QD was nearly identical (Fig. 3c), suggesting that both doses lie on the plateau of the QD dose—response curve. A further comprehensive evaluation of the relative efficacy of olodaterol 5 and 10 μg QD has now been conducted in Phase III studies, and no significant difference in efficacy between olodaterol 5 μg and olodaterol 10 μg has been found [12—15]. The lack of washout period between treatments may be considered a limitation in this study but we believe that it is justified since any residual bronchodilatory effects from the previous treatment would not have been present at the time of the 24-h pulmonary function measurements at the end of each 3-week treatment period. The benefits of conducting the trial in this manner include reducing patient observation time and maintaining the patient on active long-acting bronchodilator therapy for the entire treatment period.

Doubling the total daily dose of olodaterol 5 μg QD can also be achieved by adding an additional dose in the evening (i.e. olodaterol 5 μg BID). To our knowledge, this is the

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Table 5 gMean plasma concentrations and gCV of olodaterol after 3 weeks of treatment.

	Olodaterol 2 μg BID			Olodaterol 5 μg QD			Olodaterol 5 μg BID			Olodaterol 10 μg QD		
	n	gMean	gCV, %	n	gMean	gCV, %	n	gMean	gCV, %	n	gMean	gCV, %
$C_{pre,ss}$ (pg/mL)	—	—	—	—	—	—	24	2.92	24.3	19	2.97	23.2
$C_{0.167,ss}$ (pg/mL)	—	—	—	25	3.52	35.9	36	4.28	42.0	41	5.78	62.1

—, gMean and gCV not calculated as this parameter was available in less than one-third of treated patients.
gMean, geometric mean; gCV, geometric coefficient of variation.

Table 6 AEs by treatment following administration of olodaterol.

	Olodaterol 2 μg BID, n (%)	Olodaterol 5 μg QD, n (%)	Olodaterol 5 μg BID, n (%)	Olodaterol 10 μg QD, n (%)	Total, n (%)
All AEs	11 (23.4)	11 (23.4)	13 (28.3)	9 (19.6)	29 (61.7)
Nasopharyngitis	1 (2.1)	1 (2.1)	3 (6.5)	3 (6.5)	6 (12.8)
Cough	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	3 (6.4)
Dyspnoea	0 (0.0)	3 (6.4)	1 (2.2)	0 (0.0)	3 (6.4)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	2 (4.3)
Dysphonia	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	2 (4.3)
Arthralgia	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)
Muscle spasms	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	2 (4.3)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	2 (4.3)

Patients: 5 μg QD, $n = 47$; 2 μg BID, $n = 47$; 10 μg QD, $n = 46$; 5 μg BID, $n = 46$.

first study with a QD bronchodilator that has directly compared the 24-h FEV_1 time profile of the same nominal dose administered QD or BID. There are two points of interest with such a comparison: firstly, to what extent does the additional evening dose provide increased bronchodilation during the 12 to 24-h interval; and secondly, does increased bronchodilation at the time of morning administration confer any advantage in terms of bronchodilation during the 0 to 12-h interval.

With regard to the first question, the second 5 μg dose in the evening resulted in an additional evening peak and an increased degree of bronchodilation during the 12 to 24-h period, reflected by an increase in FEV_1 AUC_{12-24} response for olodaterol 5 μg BID compared with olodaterol 5 μg QD. When consideration is given to the typical 24-h time profile of a QD bronchodilator (i.e. a peak bronchodilating effect within 3 h post-dose, followed by a gradual decline over the 24-h dosing interval to trough values ~ 50% of peak values), the 24-h FEV_1 time profiles of olodaterol 5 μg QD and 5 μg BID are likely representatives of a general characteristic of all QD bronchodilators. However, we are not aware of any such direct comparisons being conducted for other QD bronchodilators. A recent frequency study with indacaterol in patients with asthma evaluated the 24-h FEV_1 time profile of 37.5 μg BID, 75 μg QD (registered dose for COPD in the USA) and 150 μg QD, but did not include a 75 μg BID dosing regimen. All studies with the QD anticholinergic tiotropium have only used QD dosing regimens, with no studies including a BID regimen. The BID anticholinergic aclidinium was first developed according to a QD regimen, and later switched to a BID dosing regimen after less than compelling efficacy observed in Phase III trials for the QD regimen [17—19]; however, there are no studies that have directly compared QD and BID dosing regimens of aclidinium.

Table 7 Drug-related AEs per treatment group (treated set).

	Olodaterol 2 μg BID, n (%)	Olodaterol 5 μg QD, n (%)	Olodaterol 5 μg BID, n (%)	Olodaterol 10 μg QD, n (%)	Total, n (%)
All drug-related AEs	1 (2.1)	2 (4.3)	2 (4.3)	6 (13.0)	7 (14.9)
Cough	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	3 (6.4)
Dyspnoea	0 (0.0)	2 (4.3)	1 (2.2)	0 (0.0)	2 (4.3)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	2 (4.3)
Dry throat	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (2.1)
Dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	2 (4.3)
Sensation of heaviness	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)

Patients: 5 μg QD, $n = 47$; 2 μg BID, $n = 47$; 10 μg QD, $n = 46$; 5 μg BID, $n = 46$.

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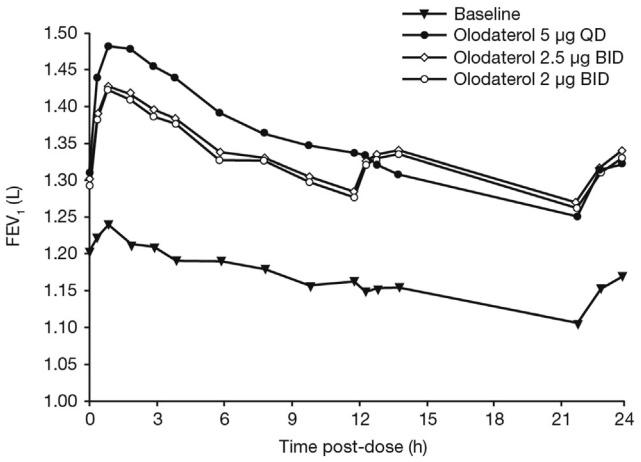

Figure 5 Adjusted mean FEV_1 over time after 3 weeks including interpolated data for the 2.5 µg BID profile.

While there was an increase in FEV_1 at the end of the 24-h interval for olodaterol 5 µg QD, this did not lead to an increase in bronchodilation during the 0 to 12-h interval; indeed, there was a small numerical increase in FEV_1 AUC_{0-12} response for olodaterol 5 µg QD compared to olodaterol 5 µg BID. Overall, the average degree of bronchodilation for olodaterol 5 µg QD and olodaterol 5 µg BID was similar.

The inclusion of two BID doses in the study offered a first, albeit limited, comparison of the BID dose-response profile of olodaterol. The observed separation of doses over both the 0 to 12-h and 12 to 24-h intervals is consistent with previous observations with olodaterol 2 µg and 5 µg QD, suggesting that the dose response of olodaterol is similar when administered according to either a QD or BID dosing regimen.

Overall, systemic exposure to olodaterol was low following treatment with olodaterol, with plasma concentration assessments at some doses and time points being below the lower limit of quantification. Urinary excretion data, however, provided evidence that exposure was dose proportional and comparable for a total daily dose irrespective of whether the study drug was administered as a single dose or split into a BID dose. Treatment with olodaterol was well tolerated, with an acceptable safety profile.

In conclusion, all dose regimens of olodaterol (2 µg, 5 µg BID; 5 µg, 10 µg QD) provided superior efficacy in FEV_1 over the 24-h dosing interval compared to baseline and were well tolerated with no safety concerns. Overall, the study provides further support for the efficacy of olodaterol 5 µg QD in COPD, with a superior bronchodilatory profile compared with olodaterol 2 µg BID, which is close to the same total daily dose, and a similar degree of bronchodilation over 24 h compared with double the daily dose administered as either a QD (10 µg) or BID (5 µg) dosing regimen.

Conflicts of interest

Guy F. Joos discloses that he has received grants and personal fees from Boehringer Ingelheim and GlaxoSmithKline, grants, personal fees and non-financial support from AstraZeneca, Novartis and Chiesi, and personal fees from Mundipharma. René Aalbers discloses honoraria from AstraZeneca, Boehringer Ingelheim, Novartis and Mundipharma. Carl Coeck, Lawrence Korducki, Alan L. Hamilton and Christina Kunz are employees of Boehringer Ingelheim. Joseph-Leon Aumann discloses no conflicts of interest.

Authors' contributions

All authors read and approved the final draft. Guy F. Joos, Joseph-Leon Aumann and René Aalbers assisted in acquisition of data, analysis and interpretation of data, and were involved in drafting the manuscript. Carl Coeck was the Clinical Trial Head and developed the design and concept of the study, and participated in the interpretation of the results and drafting of the manuscript. Lawrence Korducki was the trial statistician and was involved in developing the study design, interpretation of the data and provided critical input to the manuscript. Christina Kunz was the trial pharmacokineticist and was involved in developing the pharmacokinetic aspects of the study design, interpretation of the pharmacokinetic data and provided critical input to the manuscript. Alan L. Hamilton participated in the development of the design and concept of the study and the interpretation of the data, and was involved in drafting the manuscript.

Acknowledgements

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to, the manuscript, were involved at all stages of development and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript. This work was supported by Boehringer Ingelheim Pharma GmbH & Co. KG. Medical writing assistance was provided by Tanya Chaudry, PhD, of Complete HealthVizion, which was contracted and compensated by Boehringer Ingelheim Pharma GmbH & Co. KG.

References

[1] Guerra S. Asthma and chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol 2009;9:409—16.
[2] Celli BR, MacNee W, Committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932—46. http://dx.doi.org/10.1183/09031936.04.00014304.
[3] Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS, on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. Am J Respir Crit Care Med 2001;163:1256—76.
[4] van Noord JA, Smeets JJ, Drenth BM, Rascher J, Pivovarova A, Hamilton AL, et al. 24-hour bronchodilation following a single dose of the novel β_2-agonist olodaterol in COPD. Pulm Pharmacol Ther 2011;24:666—72.

[5] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2013. 2013. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf [accessed 05.03.14].
[6] Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β-agonists for stable COPD: a systematic review. Chest 2012;142:1104–10.
[7] Toy EL, Beaulieu NU, McHale JM, Welland TR, Plauschinat CA, Swensen A, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med 2011;105:435–41.
[8] Bouyssou T, Casarosa P, Naline E, Pestel S, Konetzki I, Devillier P, et al. Pharmacological characterization of olodaterol, a novel inhaled β_2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. J Pharmacol Exp Ther 2010;334:53–62.
[9] Cazzola M, Matera MG, Lötvall J. Ultra long-acting β_2-agonists in development for asthma and chronic obstructive pulmonary disease. Expert Opin Investig Drugs 2005;14:775–83.
[10] O'Byrne PM, van der Linde J, Cockcroft DW, Gauvreau GM, Brannan JD, FitzGerald M, et al. Prolonged bronchoprotection against inhaled methacholine by inhaled BI 1744, a long-acting β_2-agonist, in patients with mild asthma. J Allergy Clin Immunol 2009;124:1217–21.
[11] van Noord JA, Korducki L, Hamilton AL, Koker P. Four weeks once daily treatment with BI 1744 CL, a novel long-acting β2-agonist, is effective in COPD patients. Am J Respir Crit Care Med 2009;179:abs A6183.
[12] Ferguson GT, Feldman GJ, Hofbauer P, Hamilton A, Allen L, Korducki L, et al. Efficacy and safety of olodaterol once daily delivered via Respimat® in patients with GOLD 2–4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis 2014;9:629–45. http://dx.doi.org/10.2147/COPD.S61717.
[13] Feldman GJ, Bernstein JA, Hamilton A, Nivens MC, Korducki L, LaForce C. The 24-h FEV_1 time profile of olodaterol once daily via Respimat® and formoterol twice daily via Aerolizer® in patients with GOLD 2–4 COPD: results from two 6-week crossover studies. Springerplus 2014;3:419.
[14] Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, De Salvo MC, et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat® versus placebo and formoterol twice daily in patients with GOLD 2–4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis 2014;9:697–714. http://dx.doi.org/10.2147/COPD.S62502.
[15] Lange P, Aumann J-L, Hamilton A, Tetzlaff K, Ting N, Derom E. The 24 hour lung function time profile of olodaterol once daily versus placebo and tiotropium in patients with moderate to very severe chronic obstructive pulmonary disease. J Pulm Respir Med 2014;4:196. http://dx.doi.org/10.4172/2161-105X.1000196.
[16] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319–38. http://dx.doi.org/10.1183/09031936.05.00034805.
[17] Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J 2012;40:830–6.
[18] Fuhr R, Magnussen H, Sarem K, Ribera Llovera A, Kirsten A-M, Falqués M, et al. Efficacy of aclidinium bromide 400 μg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. Chest 2012;141:745–52. http://dx.doi.org/10.1378/chest.11-0406.
[19] Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF, et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). COPD 2012;9:90–101.

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